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Oncogeriatrics (part 5.)
The role of comorbidities in older patients with cancer

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Comorbidity is defined as the presence of one or more additional conditions co-occurring with primary indices. Comorbidity is common in older cancer patients. Its prevalence, however, is difficult to determine and varies by cancer site. There is no single reason for which comorbidity and cancer coexist, but chronic diseases and cancer are both common in older age and share many risk factors.

There is no consensus on how should comorbidity be measured. Even though many comorbidity indices have been developed so far, no unified, widely used instrument exists.

Patients with comorbidities have worse outcomes compared to those with no such conditions. They may experience diagnostic and therapeutic delay and be disqualified from radical treatment more often. Moreover, they are more likely to suffer from treatment-related complications and have worse overall survival.

It seems important to assess the comorbidity status as a part of individualised oncologic treatment planning. However, as data regarding its significance are insufficient and in many cases conflicting, patients with comorbidity should not be routinely considered as not fit enough for a radical treatment. Therefore, to adequately address all of the concerns that have been raised, a broader participation of older, comorbid patients in clinical trials is needed.

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Key words: older patient, comorbidity, multimorbidity, frailty

Introduction

Almost all chronic diseases are more prevalent in elderly than younger individuals, and so is cancer. That is why taking care of oncology patients who suffer from multiple, concurrent comorbidities is an everyday job [1]. Nevertheless, such patients are still often excluded from randomised controlled trials, making it difficult to generalise results and establish relevant clinical guidelines [2]. This, in turn, leads to diagnostic and treatment dilemmas. Older patients with comorbidity are often disqualified from radical therapy, receive suboptimal care, and suffer from various adverse events: prolonged hospitalisation, institutionalisation, decreased quality of life, and higher complication rates and mortality [3]. Despite the fact, that comorbidity is considered important by most clinicians, there is no consensus on definition, way to measure it, and its role in geriatric assessment. It also often gets confused with other terms, which are related to but not synonymous with comorbidity, such as multimorbidity, polypharmacy, frailty or disability [1].

Definition and etiology

The problem of comorbidity was firstly addressed in 1970 by Feinstein, who noticed its influence on the diagnostic and therapeutic process and defined it as "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient that has the index disease under study" [4]. Since that time, the term has been used in multiple studies indicating either a disease coexisting with the primary disorder simultaneously, but independently, or every additional condition, even one related to the "index" disease. The concept

of comorbidity is important not only in clinical medicine, but also in public health and epidemiology, which explains the need for different definitions and approaches to its measurement [5]. For the clinicians' purposes, it seems most appropriate to acknowledge that **comorbidity is the presence of one or more additional conditions co-occurring with a primary condition**. Regarding oncological patients, in most cases cancer is considered the primary, index disease, while other disorders are named as comorbidities.

Considering the etiology of comorbidity, Valderas et. al. [5] suggested five main pathways in which the co-existing diseases may be associated:

1. There is no etiological association between the diseases (two diseases occur by chance e.g. lung cancer and psoriasis)
2. One of the diseases is a direct cause of the other (e.g. brain tumor and epilepsy)
3. The risk factors for each disease are correlated (e.g. risk factor1: smoking → disease1: chronic pulmonary obstructive disease; risk factor2: alcohol→ disease2: Hepatocellular carcinoma)
4. The risk factors for each disease are not correlated, but each can cause either disease (e.g. risk factor 1: smoking; risk factor 2: age, disease 1: ischaemic heart disease; disease 2: lung cancer)
5. The symptoms of each disease are in fact all caused by another, undiagnosed disease (e.g. disease1: tension headaches, disease2: hypertension, disease 3: pheochromocytoma) [5].

In older patients, however, such interrelations are difficult to follow, as their comorbidities are often multiple, long-lasting and co-exist with functional decline. Nevertheless, looking for possible causes and associations between particular conditions is essential, as in some cases the onset of comorbidity can be predicted, or a single intervention may address more than one health issue. It is also worth mentioning that oncological treatment itself may cause or worsen comorbidity. While cancer often becomes a chronic condition, this mechanism seems to be of growing importance [1].

How can we measure comorbidity?

There is no "gold standard" regarding comorbidity measurement, as none of the existing approaches is optimal for all purposes. The simplest way is to divide patients into two groups: with or without comorbidity; or to simply count the prevalence of all comorbid conditions. However, defining what a comorbid condition is may be difficult, resulting in weak repeatability and the poor prognostic value of this approach. The problem may be solved by the use of comorbidity indices. The most popular ways to quantify the problem of comorbidity are simple condition counts, organ-based systems or weighted indices (Tab. I).

While choosing the measure of comorbidity, the key considerations are [16]:

1. **What is the cancer site?** As some of the measures have been developed specifically for a particular disease, it seems appropriate to use them if applicable.
2. **What is the endpoint to predict?** The indices have been developed to predict different outcome measures e.g. 10-year mortality, cancer survival, postoperative mortality etc. It would be reasonable to use the index with the highest possible validity for the particular clinical or research question.
3. **What kind of data and how much time do we have?** Some of the indices require a lot of specific information that is unavailable or assessment may be too time-consuming. The choice should be, though, adjusted to the clinical situation or research plan.

Unfortunately, there is still a great inconsistency in approach to the analysis of comorbidity status. The prognostic value, validity, reliability and feasibility of different measures is often questioned, making clinicians unclear about their usefulness and generally unwilling to use them on a regular basis [16].

Epidemiology

The burden of comorbidity in older cancer patients is of increasing concern. Its prevalence is generally high, but differs depending on the population included and research methodology (e.g. type of cancer, age range, way in which comorbidity was assessed). Regarding lung cancer, in patients aged ≥70 several authors reported that 80–83% of patients had CCI ≥1 [17–19]. In oesophageal cancer patients aged ≥65, prevalence of comorbidity (CCI ≥1) was also high and ranged from 70–80% depending on the study [20–22]. Among individuals aged 65 or more suffering from head and neck cancer, Dziemiańczyk-Pakieła et. al. reported comorbidity in 62% of patients, based on a list of diagnoses available in medical records [23]. In older patients with colon cancer (≥65 y), however, comorbidity (CCI ≥1) was present less often as its' prevalence ranged from 32–52% [24–26]. In a US study of 49 616 women with breast cancer, 23% of patients aged 85–89 and 11% of patients aged 67–69 had severe comorbidity (CCI ≥2) [27]. In general, studies with more inclusive measures of comorbidity show a higher percentage of affected patients. It also seems to be more common in those with certain cancer types, especially smoking-related cancers such as lung, head and neck or bladder cancer [28], and in reports based on questionnaires or review of medical notes, rather than in those based on administrative data [29–31]. Analysis of the prevalence of different types of comorbidity is difficult, as most authors uses indexes, rather than list all of the the diagnoses. Most likely, however, the spectrum of diseases coexisting with cancer reflects the distribution of disorders in the general populations of the elderly. For example, in a Dutch registry of patients with breast, lung, colorectal, prostate and ovarian cancer aged ≥70, most common were heart disease, cerebrovascular and peripheral vascular disease, hypertension, pulmonary disease and diabe-

Table I. A summary of the characteristics of frequently used comorbidity indices

Index name	Author, year	Clinical purpose	Items included	Severity of assessed items	Scoring	Score range
ASA	Saklad et al., 1941 Last Amended: ASA House of Delegates, 2019 [6]	to assess and communicate a patient's pre-anesthesia comorbidities. The classification system alone does not predict the perioperative risks	overall physical status	does not apply	does not apply	1–6
CIRS	Linn et al., 1968 [7]	physical impairment assessment for various clinical uses	13/14 systems	0–4	summative	0–56
KFI	Kaplan and Feinstein, 1974 [8]	to predict 5-year mortality due to the comorbid conditions in patient with type II diabetes	12 systems	1–3	highest score	1–3
CCI	Charlson et al., 1987 [9]	to predict risk of death from comorbid disease during 10-years follow-up	17 conditions	1–6	summative	0–33
ICED	Greenfield et al., 1993 [10]	to predict the impact of comorbidity and functional status on the 1-year postoperative complications and quality of life after total hip replacement	14 systems +10 functional impairments	0–4 (comorbidity) 0–2 (functional status)	highest scores of both dimensions	0–3
Satariano Index	Satariano et al., 1994 [11]	to predict the effect of comorbidity on 3-years survival in breast cancer patients	7 conditions	unweighted	condition count	0–7
Elixhauser Comorbidity Index	Elixhauser et al., 1998 [12]	assessment of comorbidity using administrative data	30 conditions	conditions analysed separately	does not apply	does not apply
Elixhauser Point System	van Walraven et al., 2009 [13]	to derive an index from Elixhauser conditions	21 conditions	β-coefficient	summ of β-coefficients	–19 to 89
ACE-27	Picirillo et al., 1996 [14]	assessment of comorbidity in oncological patients	27 conditions	1–3	highest score of single item	1–3
CPS	Evans et al., 2012 [15]	assessment of the severity of comorbid conditions in trauma patients	all known conditions + all pre-injury medications	unweighted	summative	0–n

ASA – American Society of Anesthesiologists Physical Status Classification System; CIRS – Cumulative Illness Rating Scale; KFI – Kaplan-Feinstein Index; CCI – Charlson Comorbidity Score; ICED – Index of Coexistent Disease; ACE-27 – Adult Comorbidity Evaluation-27; CPS – Comorbidity-Polypharmacy Score

tes [32]. In recent years, researchers have also tried to examine so-called patterns of comorbidity, as certain diseases seem to occur in typical clusters (e.g. cardiopulmonary, cardiovascular, metabolic, neurological/mental health etc.). This approach may facilitate development of prevention strategies and clinical practice guidelines, but considering older cancer patients, the existing data is still insufficient [33, 34].

How does comorbidity affect cancer outcomes?

Cancer outcomes may be influenced by comorbidity on many levels, starting from screening and detection, through choice of treatment, adherence and compliance, ending with treatment response and complications.

The presence of comorbid conditions may blur the classical clinical presentation of cancer, resulting in diagnostic delay. It is no surprise that diseases like dementia, alcohol dependence or other psychiatric disorders have been associated with late cancer diagnoses [33]. Also, the greater number of comorbid conditions has been shown to be associated with **longer cancer diagnostic intervals** [35]. As physicians are usually focused mostly on the chief complaint, comorbid patients may **receive screening procedures less often**. For example, that is why in a Canadian cross-sectional study, patients with depression were found to receive colorectal cancer screening recommendations less often [36]. With fewer resources and social support, older patients with chronic diseases may also **experience difficulties with travelling to medical facilities**. Moreover, such individuals (especially the oldest) may be simply less interested in undergoing life prolonging procedures [37]. On the other hand, comorbid patients are more likely to use medical services. They may undergo preventive follow-ups more often and so benefit from oncological alertness. This positive impact, however, seems only to occur in certain comorbidity types. Fleming et al. reported that women who had cardiovascular, musculoskeletal, gastrointestinal, genitourinary disease, or osteoarthritis had 7%–24% lower risk of developing

advanced breast cancer. Conversely, however, they found those with diabetes, renal, endocrine, psychiatric, haematological disease, osteoporosis, obesity and AIDS to be at 11%–20% higher risk of being diagnosed with cancer at an advanced stage [38]. Other studies analysing the use of mammography, PSA, Pap smear and colorectal cancer screening between patients with different comorbidity burdens have also had mixed results, reporting either higher or lower risk of being diagnosed with an advanced disease [39]. While cancer screening is in many ways related to comorbidity status, a common dilemma is whether a chronically ill patient may benefit from early cancer detection. Unfortunately, as no recommendations are available in this matter, they probably often get either under- or over-screened [39]. The presence of comorbidity has also been associated with **prolonged time from diagnosis to treatment**, as a certain amount of time is needed to consult the patients with other specialists or to stabilise their chronic diseases [40].

A general belief that **patients with comorbidities have poorer overall survival compared to those without comorbidities** has been confirmed by most researchers. The systematic review of observational studies, which analysed the impact of comorbidity on breast, colorectal and lung cancer outcomes, showed that in breast cancer patients the 5–7 years mortality was 1.1 to 5.8-fold higher in patients with comorbidity, among patients with colorectal cancer the 5-year mortality was 1.2 to 4.8-fold higher, and in lung cancer (1–5 years follow-up) 1.1 to 1.5-fold higher. The lowest difference in survival time in lung cancer patients was most likely due to the fact that the effect of comorbidity on the overall mortality seems to be more evident in highly curable cancers. Patnaik et al., for example, who analysed a cohort of 64 0034 women with stage I breast cancer (known for its favourable prognosis), found that in patients with serious comorbidities, the outcomes have not corresponded with survival rates of early--stage cancer, but were comparable to later-stage tumours [27]. Even though comorbidity has generally been associated with so-called "death due to causes other than cancer", several authors reported increased cancer-specific mortality in comorbid patients as well [41–43]. The question is, though, whether comorbidities may **influence the histological features of cancer**. It seems possible that chronic inflammatory state, hyperinsulinemia or immunosuppression are associated with more aggressive cancer growth and higher grade [43–45]. On the other hand, commonly prescribed drugs, such as non--steroid anti-inflammatory agents or statins, are considered to be protective against cancer [46–48].

Another concern while dealing with older, comorbid patients is the choice of treatment. According to a recent systematic review, some of the older cancer patients themselves considered comorbidity as an important reason for declining cancer treatment [49]. As far as the physicians' decisions are concerned, a common pattern, observed by most researchers, is a **higher rate of disqualifications from surgery in comorbid patients** [50, 51]. The question is, however, whether older patients with comorbidity are in fact at a higher risk of developing postoperative complications, and if so, which comorbidities are important. Unfortunately, regarding older cancer patients, data about its impact on surgical treatment effects are scarce. Most of the authors present data for patients of all ages. Yvette et al., who analysed 8583 gastrointestinal cancer patients from the Netherlands, found several comorbidities derived from CCI (cardiac disease, vascular disease and previous malignancy in colon cancer; vascular disease in rectal cancer) to be independent risk factors for 30-day mortality according to multivariate logistic regression analysis [52]. In another large study from the Netherlands (4911 colon, 2674 rectal, 2385 NSCLC and 8501 breast cancer patients), Janssen-Heijnen found that several complications occurred more often in patients with certain comorbidities, but none of them turned out to be significant in the multivariate logistic regression analysis [53]. Analysing the results of 214 patients undergoing gastrectomy, Hamakawa et.al. showed that only pulmonary (OR = 2.69) and vascular disease (OR = 5.46) were significantly associated with postoperative complications in the multivariate analysis [54]. Wang et al. reported that among 1,657 patients undergoing laparoscopy-assisted total gastrectomy the presence of comorbidity (≥1 coexisting disease) was a risk factor for local (OR = 1.20) and systemic complications (OR = 1.24). They also found specific diseases such as diabetes mellitus, anaemia, and pulmonary and renal disease to be the risk factors for abdominal bleeding, anastomotic leakage and pneumonia [53]. Nevertheless, generalising such results for the population of elderly people may be misleading. Kim et al., who have analysed the results of patients after laparoscopy-assisted distal gastrectomy found that in all the patients included, comorbidity was a predictive factor for systemic complications in the multivariate analysis. However, after dividing the patients into two subgroups (1: <60 y, 2: ≥60 y), comorbidity remained a significant risk factor (OR = 3.32) only in patients aged ≥60 [55]. In a study based on Surveillance, Epidemiology, and End Results–Medicare Registry, which included 149,622 patients aged 75 or more, CCI ≥3 was found to be a risk factor for 30-day readmission after colorectal cancer surgery (OR = 1.27) [56]. Regarding the Polish population, the authors of this review performed a logistic regression analysis among 600 individuals aged ≥65 undergoing elective high risk abdominal surgeries (60% of cancer patients) and found psychiatric (OR = 4.4) and kidney disease (OR = 2.74) to be the independent risk factors for 30-day mortality, and heart disease (OR = 1.67) to be the independent risk factor for 30-day major complications (unpublished data). For now, however, the variation in study outcomes makes it difficult to draw certain conclusions, which may be useful in clinical practice.

Moreover, comorbid patients are also **less likely to receive adjuvant therapy and to complete chemotherapy treatment**. According to existing data, comorbidity may predispose

to **development of chemotherapy-related toxicity**, so they often receive a reduced chemotherapy dose [57–60]. To assess the pharmacological treatment safety, however, data from clinical trials would be most relevant. Even though the American Society of Clinical Oncology (ASCO), Friends of Cancer Research, and the US Food and Drug Administration recently recommended changing the criteria used to exclude comorbid patients from cancer clinical trials, the presence of comorbidities is still adversely associated with trial discussions, offers and participation [61].

Conclusions

Comorbidity is common in older cancer patients. Its prevalence, however, is difficult to determine and varies by cancer site. There is no single reason for which comorbidity and cancer coexist, but chronic diseases and cancer are both common in older age and share many risk factors. Also, the treatment of one condition may be involved in the development or affect the course of another disease.

There is no consensus on how comorbidity should be measured. Even though many comorbidity indices have been developed so far, no unified, widely used instrument exists.

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